KIT FOR THE PREPARATION OF TECHNETIUM TC 99M MEBROFENIN - mebrofenin injection, powder, lyophilized, for solution

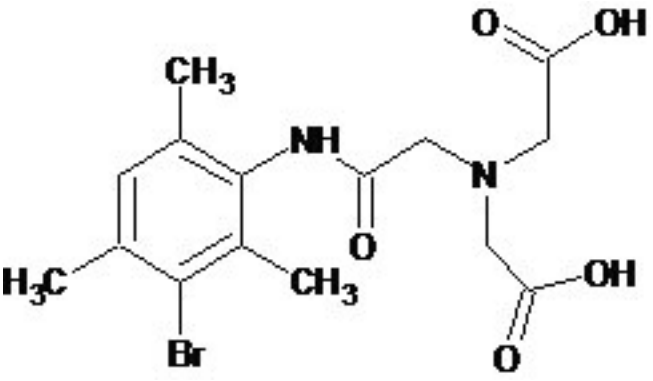
Pharmalucence, Inc.

DESCRIPTION

Each multidose reaction vial contains a nonradioactive, sterile, nonpyrogenic mixture of 45 mg mebrofenin, 0.54 mg (minimum) stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$ and 1.03 mg total tin, maximum (as stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$), not more than 5.2 mg methylparaben, and 0.58 mg propylparaben. The pH is adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture.

The pH of the reconstituted product is 4.2 to 5.7.

The structure of mebrofenin (2,2'-[[2-[(3-Bromo-2,4,6-trimethylphenyl)-amino]-2-oxoethyl]imino] bisacetic acid) is shown below:



Molecular Weight = 387.23

When sterile, pyrogen-free sodium pertechnetate Tc 99m injection is added to the vial, the diagnostic agent Technetium Tc 99m Mebrofenin is formed for administration by intravenous injection.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that is useful for detection and imaging studies is listed in Table 1.

TABLE 1

Principal Radiation Emission Data		
Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, (1981) p. 108.

External Radiation

The specific gamma ray constant for Tc 99m is 0.78 R/hour-millicurie at 1 cm. The first half value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE 2

Radiation Attenuation by Lead Shielding	
Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of technetium Tc 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart: Tc 99m half-life 6.02 hours			
Hours	Fraction Remaining	Hours	Fraction Remaining

0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501	18	0.126

*Calibration time

CLINICAL PHARMACOLOGY

Mebrofenin is an iminodiacetic acid (HIDA) derivative with no known pharmacologic action at the recommended doses.

Following intravenous administration in normal subjects, Technetium Tc 99m Mebrofenin was rapidly cleared from the circulation. The mean percent injected dose remaining in the blood at 10 minutes was 17%. The injected activity was cleared through the hepatobiliary system with visualization of the liver by 5 minutes and maximum liver uptake occurring at 11 minutes post-injection. Hepatic duct and gallbladder visualization occurred by 10 to 15 minutes and intestinal activity was visualized by 30 to 60 minutes in subjects with normal hepatobiliary function. The mean percent injected dose excreted in the urine during the first 3 hours was 1% (0.4 to 2.0%).

Elevated serum bilirubin levels increase renal excretion of Tc 99m HIDA agents. In two studies in which Tc 99m Mebrofenin was administered to patients having mean elevated serum bilirubin levels of 9.8 mg/dL (1.7 to 46.3 mg/dL), the mean percent injected dose excreted in the urine during the first 3 hours was 3% (0.2 to 11.5%). The mean percent injected dose excreted in the urine during 3-24 hours was 14.9% (0.4 to 34.8%).

In jaundiced patients, the percent injected dose remaining in the blood at 10 minutes may be twice as high or more than the level in normals. Hepatobiliary transit may be delayed and visualization times increased. As a consequence, the quality of the images obtained frequently diminishes.

INDICATIONS AND USAGE

Technetium Tc 99m Mebrofenin is indicated as a hepatobiliary imaging agent.

CONTRAINDICATIONS

Hypersensitivity to this compound.

WARNINGS

The theoretical possibility of allergic reactions should be considered in patients who receive multiple doses.

PRECAUTIONS

General

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Mebrofenin and are not to be administered directly to the patient.

Delayed or non-visualization of the gallbladder may occur in the immediate post-prandial period or after prolonged fasting or parenteral feeding. Functional biliary obstruction may accompany chronic cholecystitis or pancreatitis. In addition, patients with hepatocellular disease may show nonvisualization or delayed visualization of the gallbladder. Delayed intestinal transit may also be noted in such patients. Juvenile hepatitis may be associated with gallbladder nonvisualization and the failure to visualize activity in the intestine. Administration of meperidine or morphine may delay intestinal transit of the imaging agent and may result in nonvisualization. Septic patients may show absent or delayed hepatobiliary clearance. Thus, a positive finding does not of itself permit a differential diagnosis of any of the above conditions and should be evaluated in the light of the total clinical picture and results of other diagnostic modalities.

The components of the kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the pertechnetate solution and the withdrawal of doses for patient administration.

The Technetium Tc 99m labeling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m supply may, thus, adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to ensure minimum radiation exposure to occupational workers.

Tc 99m Mebrofenin should be formulated no more than 6 hours prior to clinical use.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Mebrofenin may affect fertility in males or females.

Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with Technetium Tc 99m Mebrofenin. It is also not known whether Technetium Tc 99m Mebrofenin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m Mebrofenin should be given to a pregnant woman only if the expected benefits to be gained clearly outweigh the potential hazards.

Nursing Mothers
Technetium Tc 99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feedings.

Pediatric Use
Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Urticaria and rash have been rarely reported with the use of Technetium Tc 99m Mebrofenin since market introduction. Rare cases of chills and nausea have been reported with related compounds. Infrequently, death has been reported in association with the use of this class of agents.

DOSAGE AND ADMINISTRATION
The suggested intravenous dose range of Technetium Tc 99m Mebrofenin in the average patient (70 kg) is:

Nonjaundiced patient: 74 - 185 MBq (2-5 mCi)

Patient with serum bilirubin

level greater than 1.5 mg/dL: 111-370 MBq (3-10 mCi)

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.
The patient should be in a fasting state, 4 hours is preferable. False positives (non-visualization) may result if the gallbladder has been emptied by ingestion of food.
An interval of at least 24 hours should be allowed before repeat examination.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

RADIATION DOSIMETRY
The estimated absorbed radiation doses[1,2] to organs and tissues of an average subject (70 kg) from an intravenous injection of 370 MBq (10 millicuries) of Technetium Tc 99m Mebrofenin are shown in Table 4.
TABLE 4

Estimated Absorbed Radiation Doses†				
	Normal Subjects*		Severely Jaundiced Patients**	
Tissue	mGy/ 370 MBq	rads/ 10 mCi	mGy/ 370 MBq	rads/ 10 mCi
Total Body	2.0	0.2	1.7	0.17
Liver	4.7	0.47	8.1	0.81
Gallbladder Wall	13.7	1.37	12.5	1.25
Small Intestine	29.9	2.99	16.0	1.60
Upper Large Intestine Wall	47.4	4.74	24.8	2.48
Lower Large Intestine Wall	36.4	3.64	19.7	1.97
Kidney	2.2	0.22	1.9	0.19
Urinary Bladder Wall	2.9	0.29	24.2	2.42
Ovaries	10.1	1.01	6.4	0.64

Testes	0.5	0.05	1.1	0.11
Red Marrow	3.4	0.34	2.5	0.25

†Method of Calculation:
(1) Loberg, M.D., Buddemeyer, E.V.: Application of pharmacokinetic modeling to the radiation dosimetry of hepatobiliary agents. In Third International Radiopharmaceutical Dosimetry Symposium, FDA No. 81-8166, U.S. Department of Health and Human Services, Public Health Service, FDA, Bureau of Radiological Health, Rockville, MD, (1981) pp. 318-332.
(2) Values for S: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).
* Bilirubin <1.5 mg/dL
Calculations assume that 98% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.
** Bilirubin >10 mg/dL (mean 21.8 mg/dL)
Calculations assume that 66% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

HOW SUPPLIED
Kit for the Preparation of Technetium Tc 99m Mebrofenin is supplied in kits of 5 or 30 reaction vials. Each vial contains a sterile, nonpyrogenic lyophilized mixture of 45 mg mebrofenin, 0.54 mg (minimum) stannous fluoride dihydrate $SnF_2 \cdot 2H_2O$ and 1.03 mg total tin, maximum (as stannous fluoride dihydrate $SnF_2 \cdot 2H_2O$), not more than 5.2 mg methylparaben, and 0.58 mg propylparaben. The pH has been adjusted with hydrochloric acid or sodium hydroxide prior to lyophilization. The lyophilized vial contents are sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 4.2 to 5.7.
Pharmalucence, Inc.
10 DeAngelo Drive
Bedford, MA 01730
781-275-7120

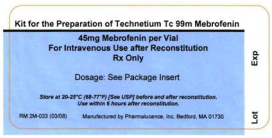
Kit Contents
5 or 30 sterile multidose reaction vials.
12 or 72 radiation labels for Technetium Tc 99m Mebrofenin (for 5 or 30 vial kits, respectively).
1 package insert.

Preparation
Preparation of Technetium Tc 99m Mebrofenin is done by the following aseptic procedure:
1. Waterproof gloves should be worn during the preparation procedure.
2. Place reaction vial in an appropriate lead shield.
3. Swab the rubber closure of the reaction vial with a germicide.
4. Inject 1 to 5 mL sterile additive free sodium pertechnetate Tc 99m injection containing up to 3700 MBq (100 mCi) Tc 99m into the reaction vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution. NOTE: If sodium pertechnetate Tc 99m injection must be diluted for use with Kit for the Preparation of Technetium Tc 99m Mebrofenin, only preservative free Sodium Chloride Injection USP should be used.
5. Secure the lead shield cover. Swirl the vial gently to mix contents and let stand for 15 minutes.
6. Record the date and time of preparation on radiation label.
7. Affix radiation label to shield.
8. Examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
9. Measure the radioactivity by a suitable calibration system and record on the shield label prior to patient administration.
10. Withdraw material with a sterile lead shielded syringe for use within 6 hours of preparation.

Storage
Store the kit as supplied at 20-25ºC (68-77ºF) [See USP] prior to and following reconstitution. Use within 6 hours of reconstitution.
Rx only
NDC-45567-0455-1 (5 Vial Kit)
NDC-45567-0455-2 (30 Vial Kit)
This reagent kit for the preparation of a radiopharmaceutical is approved for use by persons licensed pursuant to section 120.547, Code of Massachusetts Regulation 105, or under equivalent license of the U.S. Nuclear Regulatory Commission or an Agreement State.
Manufactured By:
Pharmalucence, Inc.

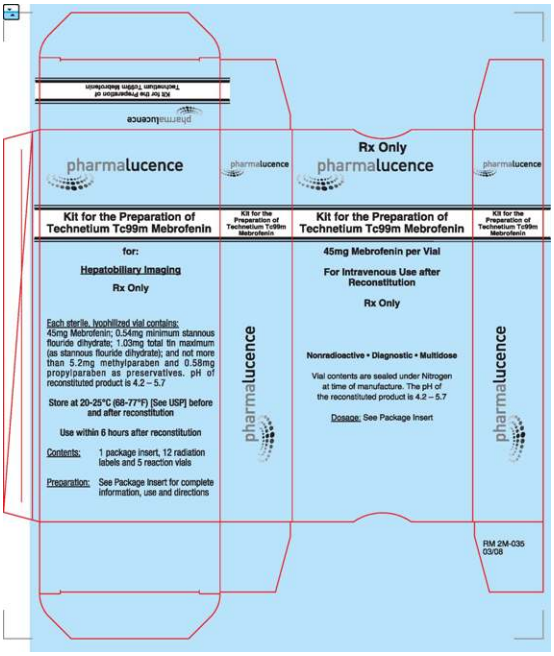
10 DeAngelo Drive
Bedford, MA 01730
1-800-221-7554
(For International call 781-725-7120)
www.pharmalucence.com
RM 2M-032
03/08

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 5 VIAL CONTAINER (10 ML)
NDC 045567-0455-1
Kit for the Preparation of Technetium Tc99m Mebrofenin
45mg Mebrofenin per Vial
For Intravenous Use after Reconstitution
Rx Only
Dosage: See Package Insert
Store at 20-25°C (68-77°F) [See USP] before and after reconstitution.
Use within 6 hours after reconstitution.
Manufactured by Pharmalucence, Inc. Bedford, MA 01730
Lot
Exp

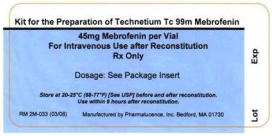


PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 5 VIAL CARTON
NDC 045567-0455-1
Kit for the Preparation of Technetium Tc99m Mebrofenin
45mg Mebrofenin per Vial
For Intravenous Use after Reconstitution
Rx Only
Nonradioactive
Diagnostic
Multidose
Vial contents are sealed under Nitrogen at time of manufacture. The pH of the reconstituted product is 4.2 - 5.7
Dosage: See Package Insert
Manufactued By:
Pharmaluence, Inc.
10 DeAngelo Drive, Bedford, MA 01730
For Customer Service call: 1-800-221-7554

Kit for the Preparation of Technetium Tc99m Mebrofenin
for:
Hepatobiliary Imaging
Rx Only
Each sterile, lyophilized vial contains:
45mg Mebrofenin; 0.54mg minimum stannous fluoride dihydrate; 1.03mg total tin maximum (as stannous fluoride dihydrate); and not more than 5.2mg methylparaben and 0.58mg propylparaben as preservatives. pH of reconstituted product is 4.2 - 5.7
Store at 20-25°C (68-77°F) [See USP] before and after reconstitution
Use within 6 hours after reconstitution
Contents: 1 package insert, 12 radiation labels and 5 reaction vials
Preparation: See Package Insert for complete information, use and directions



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 30 VIAL CONTAINER (10 ML)
NDC 045567-0455-2
Kit for the Preparation of Technetium Tc99m Mebrofenin
45mg Mebrofenin per Vial
For Intravenous User after Reconstitution
Rx Only
Dosage: See Package Insert
Store at 20-25°C (68-77°F) [See USP] before and after reconstitution.
Use within 6 hours after reconstitution.
Manufactured by Pharmalucence, Inc. Bedford, MA 01730
Lot
Exp



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 30 VIAL CARTON
NDC 045567-0455-2
Kit for the Preparation of Technetium Tc99m Mebrofenin
45mg Mebrofenin per Vial
for
Hepatobiliary Imaging
For Intravenous Use after Reconstitution
Rx Only
Nonradioactive
Diagnostic
Multidose
Vial contents are sealed under Nitrogen at time of manufacture. The pH of the reconstituted product is 4.2 - 5.7
Dosage: See Package Insert
Manufactued By:
Pharmaluence, Inc.
10 DeAngelo Drive, Bedford, MA 01730
For Customer Service call: 1-800-221-7554
Contents: 1 Package Insert, 72 radiation labels and 30 reaction vials

Each sterile, lyophilized vial contains: 45mg Mebrofenin; 0.54mg minimum stannous fluoride dihydrate; 1.03mg total tin maximum (as stannous fluoride dihydrate); and not more than 5.2mg methylparaben and 0.58mg propylparaben as preservatives. pH of reconstituted product is 4.2 - 5.7

Store at 20-25°C (68-77°F) [See USP] before and after reconstitution

Use within 6 hours after reconstitution

Preparation: See Package Insert for complete information, use and directions